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Risk of diabetes and dyslipidemia during clozapine and other antipsychotic drug treatment in schizophrenia in Iceland

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Abstract

Background

Type 2 diabetes (T2D) and raised blood lipids are associated with the use of antipsychotics, not least clozapine.

Aims

To describe the prevalence of high blood glucose levels, T2D and dyslipidemia in association with the use of clozapine or other antipsychotics in patients with schizophrenia in Iceland.

Method

We identified 188 patients treated with clozapine and 395 patients never treated with clozapine by searching the electronic health records of Landspitali, the National University Hospital. The comparison group consisted of Icelandic population controls. We obtained data on blood glucose, HbA1c and blood lipid levels from these health records.

Results

The prevalence of T2D was 14.3% in the clozapine group, where the average age was 51.2 years, and 13.7% in the never-on-clozapine group where the average age was 58.6 years. Males on clozapine were 2.3 times more likely and females 4.4 times more likely to have developed T2D than controls from an age-adjusted Icelandic cohort while males on other antipsychotics were 1.5 times more likely and females 2.3 times as likely to have T2D. Having ever been measured with a high blood sugar level, over 13 mmol/l, was strongly associated with T2D. Only one case of ketoacidosis was identified. Triglyceride levels were significantly higher in both treatment groups compared to controls in the age-adjusted Icelandic cohort.

Conclusions

Clinicians must take active steps to reduce the risk of T2D and raised triglycerides in patients with schizophrenia. Antipsychotics were associated with a greater risk of T2D developing in females compared to males.

Keywords: schizophrenia, clozapine, diabetes, dyslipidemia, metabolic

Running title: Diabetes and dyslipidemia with antipsychotic drugs

Background

Second generation antipsychotics (SGA) have been widely reported to increase the risk of T2D, obesity and dyslipidemia during the treatment of psychotic disorders such as schizophrenia (1).

Most antipsychotics have been associated with weight gain, at least in some patient populations. Olanzapine and clozapine have the highest risk of weight gain (1). Ziprasidone, aripiprazole and amisulpride have the lowest reported risk of weight gain but risperidone and quetiapine are intermediate in this regard (1). Obesity is the main modifiable risk factor for T2D and 80% of patients are overweight at diagnosis (2). Females may be at higher risk for weight gain (3). Some patients are particularly prone to weight gain and it has been reported that a common variant near the melanocortin 4 receptor gene is associated with severe SGA-associated weight gain (4). It has also been reported that when switching from an antipsychotic with a high risk for weight gain to an antipsychotic with a less risk for weight gain, patients find it easier to lose weight in due course (5).

Metabolic syndrome has been shown to be more common with patients treated with clozapine (51.9%) than with other antipsychotics in schizophrenia (32.5%) (6). In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, the proportion of males with metabolic syndrome was 36.6% but 54.2% for females (7). In an Icelandic study of patients with schizophrenia with a mean age of 50 years the prevalence of metabolic syndrome was found to be 57% compared to 14% in the general population (8). In the same study the prevalence of T2D was 15%.

The risk of T2D is not the same for all second generation antipsychotics. Aripiprazole and ziprasidone are associated with the lowest risk and some studies report no added risk for patients on these drugs (9-11). The risk for T2D has been reported to be dose dependent for some antipsychotics such as olanzapine, risperidone and quetiapine (10).

Patients treated with antipsychotics have an estimated 10 times the risk of developing ketoacidosis compared to the normal population (12). Increased risk of ketoacidosis during clozapine treatment has been documented in case reports (13).

Dyslipidemia, which is a well known risk factor for coronary artery disease is characterized by elevated triglycerides, high cholesterol, high levels of low density lipoprotein (LDL) and low levels of high density lipoprotein (HDL) (14). Clozapine and olanzapine have been associated with an increase in cholesterol and triglyceride levels in patients with schizophrenia (15-18). These drugs have also been shown to decrease HDL-cholesterol (16). Risperidone has also been associated with increased triglyceride levels (16). Other antipsychotics like amisulpride and ziprasidone have been reported to have a more favorable effect on blood lipid profiles and may therefore be preferable for patients who have developed the metabolic syndrome (18).

Life expectancy in schizophrenia is reduced by more than 20 years, mainly due to relatively poor physical health, although a high risk for suicide also has an impact (19). Antipsychotic drug use in schizophrenia is associated with higher life expectancy even though antipsychotics are associated with metabolic side effects (19). Clozapine has been reported to have more adverse effects than other antipsychotics but there is evidence that clozapine reduces the risk of suicide as well as overall mortality compared to other antipsychotics (19). The risk of death from cardiovascular disease for patients on clozapine may be dependent on genetic makeup, diet and social factors because the rate of death from cardiovascular disease in Hispanic and African-American patients receiving clozapine has been reported to be 4.3 and 11.5 times the rate in Caucasians, respectively (17).

Aims

The aim of this study is to analyze the prevalence of diabetes and dyslipidemia in a well-described sample of Icelandic schizophrenia patients on clozapine as well as patients with schizophrenia who have never been on clozapine. In order to assess the standardized morbidity ratio of diabetes and dyslipidemia for both groups the results will be contrasted with prevalence figures based on Icelandic population cohorts.

Methods

Study population

The study population has been described in a previous article by the same authors (20). The study is a part of an ongoing study of psychotic disorders in the Department of Psychiatry at Landspitali University Hospital (LUH), focusing on patients with schizophrenia and bipolar disorder. In this study we looked at patients in the LUH cohort who were alive on 1.1.2003 and who had a confirmed diagnosis of schizophrenia according to the "Schedules for Affective Disorder and Schizophrenia-Lifetime version" (SADS-L) (21). In total there were 611 patients who met the criteria. All participants gave written informed consent. We identified in this way 201 patients with schizophrenia who had used clozapine and 410 patients with schizophrenia who had never used clozapine but been treated with other antipsychotics.

Figure 1. Description of study cohort in the study period of 1.1.1998 – 21.11.2014

Metabolic disorders

T2D was diagnosed if the patients had a formal diagnosis of T2D, HbA1C >=6.5% on two separate occasions or two measurements of fasting plasma glucose over 12.6 mg/l (7.0 mmol/l). The patient's primary physician was contacted if additional blood samples were needed to assess if the patients had developed T2D. High risk of T2D was labelled if the last measurement of HbA1c was in the range 6.0% to 6.4%. Ketoacidosis was diagnosed if a clinical diagnosis of ketoacidosis could be confirmed. In accordance with the ATP-III guidelines we defined LDL in the range 160-189mg/dl (4.13-4.89 mmol/l) as high LDL and LDL over 190mg/dl (4.90 mmol/l) as very high (14). Total cholesterol over 200mm/dl (5.17 mmol/l) was defined as high. Triglycerides between 200-499mg/dl (2.56-5.63 mmol/l) were defined as high and triglycerides over 500mg/dl (5.65 mmol/l) as very high. When analyzing statin use while patients were taking clozapine, we used the last known medication regimen stated in the medical notes before the end of follow-up or the date that the patient discontinued clozapine.

A keyword search in the EHR was done, to find medical notes where the metabolic disorders were mentioned. For diabetes we looked for "diabetes", "*sykursýki*", "metformin", "glucophage" and "T2D".

For Ketoacidosis we looked for “ketoacidos” and “ketona”. For dyslipidemia the blood lipid measurements in the blood test database were analyzed. All blood measurements of: HbA1c, glucose, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were collected electronically via the EHR. When assessing blood lipids the latest measurements of blood lipids were used. For patients on clozapine we used the latest blood measurements while the patient had been receiving clozapine.

Statistical analysis

Statistical analyses were performed with STATA, version 13. A Cox proportional hazard model was used to assess the association of blood sugar values over 13 mm/l with “average time at risk”, “clozapine ever used” and “T2D at the end of follow up”. Time at risk for patients on clozapine was defined as the start of clozapine treatment or the start of the study period if the patients had started clozapine treatment before the onset of the study period, until one of the following end points was reached: a measurement of blood sugar value over 13 mm/l, end of the study period, patient died or when the patient discontinued clozapine treatment. Time at risk for patients never on clozapine was defined as the onset of the study period, until one of the following end points was reached: a measurement of blood sugar value over 13 mm/l, end of the study period or when the patient died. We tested for the proportional hazards assumption using the estat phtest in STATA.

The prevalence of T2D and blood lipid levels were compared to a population of Icelanders using data from the Icelandic National Heart Association making use both of data from the AGES (22) and the REFINE (Risk Evaluation For INfarct Estimates) studies. The prevalence of T2D and blood lipid levels were calculated for men and women by age ranges of five years from 25 to 90. The prevalence of T2D and blood lipid levels in different age ranges of the Icelandic population group was used to calculate the expected prevalence of T2D and blood lipid levels. This comparison indicated what prevalence of T2D and lipid levels could be expected if comparable age groups were examined in the general population.

Results

Prevalence of diabetes in patients with schizophrenia

The observed prevalence of T2D was 14.3% in the clozapine group, where the average age was 51.2 years, whereas the observed prevalence of T2D was 13.7% in the never-on-clozapine group where the average age was 58.6 years. Table 1 describes the prevalence of diabetes in the cohort in more detail. The age adjusted difference of T2D for the groups is shown in table 2.

In the clozapine group the prevalence of T2D for females was 16.1%, which was higher than for males where the proportion of T2D was 13.6% but the difference was not significant (p = 0.32).

Table 1 approximately here

Prevalence of T2D in patients with schizophrenia compared to Icelandic population controls

Table 2 shows that T2D was more common in patients with schizophrenia than in Icelandic population controls adjusted for sex and age. The standardized morbidity ratio for T2D was highest for females on clozapine, 4.4.

Table 2 approximately here

Time from onset of clozapine treatment to diabetes

The average time from initiation of clozapine treatment to diagnosis of T2D was 7.7 years (SD = 6.7) and the median time was 7.3 years in these patients with schizophrenia. The range of T2D diagnosis was from 43 days to 25.3 years.

Ketoacidosis and high blood sugar

Table 3 demonstrates that not a single case of ketoacidosis was identified in the group of patients on clozapine and only a single case in the never-on-clozapine group. Therefore, the proportion of ketoacidosis in the whole group was only 0.2% (1/583). The highest glucose measurement found in the group of patients without T1D or T2D was 15.0 mmol/l.

Table 3 approximately here

Table 4 shows that T2D was associated with blood sugar values over 13 mmol/l, in both males and females. Clozapine use was not associated with blood sugar values over 13. Lower age was significantly associated with glucose values over 13 mm/l in males but not females.

Table 4 approximately here

Blood lipids

In table 5 the results of blood lipid measurements are presented for 144 patients in the clozapine group and 258 patients in the never-on-clozapine group. In the clozapine group 9 patients (6%) had very high levels of LDL (over 4.9 mmol/l) and a similar proportion was observed in the in the never-on-clozapine group, 13 patients (5%). In the clozapine group 89 patients (62%) had high levels of total cholesterol (over 5.2 mmol/l) and 133 (52%) in the never-on-clozapine group. In the clozapine group 11 patients (8%) had total cholesterol below 4 mmol/l, but 34 (13%) in the never-on-clozapine group. No patient in the never-on-clozapine group had very high levels of triglycerides (over 5.65 mmol/l) but 5 patients (3%) in the clozapine group were observed to have such high levels.

Table 5 approximately here

For medication other than clozapine we had detailed information for 154 patients and of these, 16 were using statins (10%) for high cholesterol and one patient (1%) was using a fibrate drug to lower triglycerides levels.

Conclusions

The results of this study indicate that treatment with clozapine increases the risk of T2D 4.4 fold for females and 2.3 fold for males in patients with schizophrenia. This gender difference has been reported for patients with schizophrenia in a large US study for patients in the Medicare and Medicaid systems (23) but the authors have not found this to be reported before for patients on clozapine. High blood sugar (over 13 mmol/l) was not associated with clozapine use after correcting for TD2 and age in our sample. Ketoacidosis was rare in our sample with only one case identified among 583 patients during follow up lasting on average 9.2 years for those on clozapine and 13.8 years for those never on clozapine. That result is similar to what was found in a study by the US Veterans Affairs (24) where only 0.2% of patients with schizophrenia were hospitalized with ketoacidosis. Triglyceride levels were elevated both in the clozapine group and in the never-on-clozapine group compared to the standard population which is consistent with results described in a review article by Newcomer (1). HDL was lower in the clozapine group compared to the Icelandic population but the effects of clozapine on cholesterol are less clear in the literature than the effects on triglycerides (1). The changes in blood lipids are modest and usually do not require treatment with statins in primary prevention (14) so more emphasis should be on diagnosing and treating T2D than dyslipidemia.

Type 2 diabetes

Females had a higher standardized morbidity ratio of T2D than males after adjustment for age and sex. The standardized morbidity ratio of T2D for females on clozapine was 4.4 compared to 2.3 in males (female/male ratio of 1.9) and for patients with schizophrenia who had never been treated with clozapine, it was 2.6 for females and 1.5 for males (female/male ratio of 1.7). This gender difference for T2D in schizophrenia in general has been reported in other studies. One possible contribution or explanation for this sex difference is that clozapine plasma concentration in females has been reported to be on average 17% higher in females than in males (25). A large Medicaid study has reported clozapine to be significantly associated with higher rates of T2D than other antipsychotics (26). In this study of patients treated with clozapine, the combined prevalence of T1D, T2D and high risk of T2D was 23.5% for males and 32.1% for females. This indicates an overall higher risk of glucose dysregulation for females than for males on clozapine treatment.

The proportion of patients at a high risk of developing T2D was twice as high in the clozapine group as in the never-on-clozapine group, 11.7%, compared to 5.8%. As one would expect, patients with treatment resistant schizophrenia treated with clozapine were more often in contact with the LUH and had more frequent measurements of HbA1c done than patients never on clozapine.

In total there were 27 patients ever treated with clozapine diagnosed with T2D and 16 (59%) of them were diagnosed with T2D during clozapine treatment. Of the other 11 patients 6 (22%) were diagnosed before clozapine treatment started and 5 (19%) after clozapine treatment had been discontinued. This indicates how complicated it is to assess the causality of clozapine-induced T2D in patients with schizophrenia. In a previous study by the authors on the clozapine group we reported that two thirds of patients taking clozapine were taking more than one antipsychotic and used a relatively high WHO defined daily dose (DDD), 1.67, which could also add to the risk of T2D (20). Patients treated with clozapine are the most severely ill patients with schizophrenia and their lifestyle behavior may place them at greater risk of T2D than the lifestyles of other patients with the same diagnosis (27). It is very difficult to control fully for these factors, so treatment resistance itself might be an important risk factor for T2D.

We found 10 patients in the clozapine group who had used metformin to reduce the risk of weight gain but did not have diabetes. That constitutes 5.3% of all patients on clozapine. Metformin can be used to counteract the metabolic side effects of clozapine (28). This high use of metformin in our cohort without a diagnosis of diabetes indicates that diabetes drug use cannot be used reliably as a proxy for the diagnosis of T2D in clinical samples.

Ketoacidosis and high blood sugar

Ketoacidosis was a very rare event in our cohort because only one patient out of 583 had developed ketoacidosis and that was a patient who had T1D. We analyzed with a Cox proportional hazards model if high blood glucose (over 13 mmol/l) was associated with clozapine treatment using patients with schizophrenia who had never been treated with clozapine for comparison. Clozapine as such was in fact not associated with high blood glucose in all the available blood samples but the main risk factor for high blood glucose was a diagnosis of diabetes. Accordingly, the risk of ketoacidosis during antipsychotic treatment

seems very small, especially if the patients do not have type 1 diabetes. In a large study from the US Veterans Affairs 0.2% of patients on antipsychotics were hospitalized because of ketoacidosis which is the same result as in our study but in that study the risk was highest for patients on clozapine where it was 2% which is higher than we observed in our study (24).

Blood lipids

Our results show that antipsychotics, especially clozapine, have more adverse effects on triglyceride values than on cholesterol as has previously been reported (1, 29). HDL cholesterol was lower both in the clozapine group and in the never-on-clozapine group but that was only statistically significant in the clozapine group.

In the clozapine group 144 out 188 patients (77%) had at least one measurement of blood lipids done during clozapine treatment. Most guidelines on metabolic monitoring for patient on antipsychotics recommend that all patients receiving antipsychotic treatment should have blood lipids measured regularly (30). It has been reported that the impact of clinical guidelines on screening and monitoring is minimal to poor (30). One of the issues with the lipid monitoring might be that recent guidelines only support statin treatment to lower blood lipids for very high levels of LDL (over 4.90 mmol/l), that is if the patients do not have a diagnosis of T2D, atherosclerotic cardiovascular disease or at least a 7.5% risk of developing atherosclerotic cardiovascular disease in the next 10 years (14). In our sample of patients on clozapine, where the average age was 51.2 years, only 6% of patients had LDL levels over 4.9 mmol/l. Recent meta-analyses for statin use in primary prevention do report reduced total mortality (31, 32). The proportion of patients using statins in our clozapine group was 10% which is the same ratio as in a Danish cohort study from 2007 on patients with schizophrenia treated with clozapine (33). In our sample the LDL and cholesterol was essentially the same in the clozapine group, the never-on-clozapine group and in the age and sex matched Icelandic population controls. Screening in the schizophrenia groups would therefore probably not support more statin treatment than screening the Icelandic population. It is therefore unlikely that a young patient diagnosed with schizophrenia, who has neither diabetes nor atherosclerotic cardiovascular disease will have statins prescribed.

There are some limitations to this study. It is a retrospective comparative analysis of patients that have been treated at a national university hospital so the results may not generalize fully to patients with less severe forms of schizophrenia who are not in contact with mental health services. The patients on clozapine were significantly younger (51.2 years) than those never treated with clozapine (58.1 years). By definition patients treated with clozapine are suffering from a more severe and a more treatment-resistant form of schizophrenia so the clozapine is not the only difference between these two groups. The strengths of the study include the screening availability of electronic health records over long perionds, full access to all patient records at LUH over two decades in a hospital where over 90% of all patients with schizophrenia have been treated for the past decades.

Clinicians need to be aware of the risk of T2D developing for patients with schizophrenia, in particular for females on clozapine treatment. Regular measurements of fasting glucose and HbA1c should be done, at least once a year. There is less evidence to support annual measurements of blood lipids, especially for patients that are on a stable antipsychotic treatment unless blood lipids are elevated or the patient has a diagnosis of atherosclerotic cardiovascular disease or T2D. As patients with schizophrenia are at a very high risk of developing atherosclerotic cardiovascular disease (34) more research is needed to assess whether statins should be used more for primary prevention in patients with schizophrenia.

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References

1. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs. 2005;19 Suppl 1:1-93.

2. Haslam DW, James WP. Obesity. Lancet. 2005;366(9492):1197-209.

3. Seeman MV. Secondary effects of antipsychotics: women at greater risk than men. Schizophr Bull. 2009;35(5):937-48.

4. Malhotra AK, Correll CU, Chowdhury NI, Müller DJ, Gregersen PK, Lee AT, et al. Association between common variants near the melanocortin 4 receptor gene and severe antipsychotic drug-induced weight gain. Arch Gen Psychiatry. 2012;69(9):904-12.

5. Newcomer JW, Campos JA, Marcus RN, Breder C, Berman RM, Kerselaers W, et al. A multicenter, randomized, double-blind study of the effects of aripiprazole in overweight subjects with schizophrenia or schizoaffective disorder switched from olanzapine. J Clin Psychiatry. 2008;69(7):1046-56.

6. Mitchell AJ, Vancampfort D, Sweers K, van Winkel R, Yu W, De Hert M. Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders--a systematic review and meta-analysis. Schizophr Bull. 2013;39(2):306-18.

7. McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophr Res. 2005;80(1):19-32.

8. Sveinsson O, Thorleifsson K, Aspelund T, Kolbeinsson H. [A study of risk factors for cardiovascular disease among schizophrenic patients using the rehabilitation mental health services at Kleppur]. Laeknabladid. 2012;98(7-8):399-402.

9. Association AD, Association AP, Endocrinologists AAoC, Obesity NAAftSo. Consensus development conference on antipsychotic drugs and obesity and diabetes. J Clin Psychiatry. 2004;65(2):267-72.

10. Ulcickas Yood M, Delorenze GN, Quesenberry CP, Oliveria SA, Tsai AL, Kim E, et al. Association between second-generation antipsychotics and newly diagnosed treated diabetes mellitus: does the effect differ by dose? BMC Psychiatry. 2011;11:197.

11. Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naïve schizophrenia patients. Neuropsychopharmacology. 2010;35(9):1997-2004.

12. Polcwiartek C, Vang T, Bruhn CH, Hashemi N, Rosenzweig M, Nielsen J. Diabetic ketoacidosis in patients exposed to antipsychotics: a systematic literature review and analysis of Danish adverse drug event reports. Psychopharmacology (Berl). 2016.

13. Nihalani ND, Tu X, Lamberti JS, Olson D, Olivares T, Costea GO, et al. Diabetic ketoacidosis among patients receiving clozapine: a case series and review of socio-demographic risk factors. Ann Clin Psychiatry. 2007;19(2):105-12.

14. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(25 Suppl 2):S1-45.

15. Wu RR, Zhao JP, Liu ZN, Zhai JG, Guo XF, Guo WB, et al. Effects of typical and atypical antipsychotics on glucose-insulin homeostasis and lipid metabolism in first-episode schizophrenia. Psychopharmacology (Berl). 2006;186(4):572-8.

16. Wirshing DA, Boyd JA, Meng LR, Ballon JS, Marder SR, Wirshing WC. The effects of novel antipsychotics on glucose and lipid levels. J Clin Psychiatry. 2002;63(10):856-65.

17. Henderson DC, Nguyen DD, Copeland PM, Hayden DL, Borba CP, Louie PM, et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. J Clin Psychiatry. 2005;66(9):1116-21.

18. Rettenbacher MA, Ebenbichler C, Hofer A, Kemmler G, Baumgartner S, Edlinger M, et al. Early changes of plasma lipids during treatment with atypical antipsychotics. Int Clin Psychopharmacol. 2006;21(6):369-72.

19. Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). Lancet. 2009;374(9690):620-7.

20. Ingimarsson O, MacCabe JH, Haraldsson M, Jónsdóttir H, Sigurdsson E. Clozapine treatment and discontinuation in Iceland: A national longitudinal study using electronic patient records. Nord J Psychiatry. 2016;70(6):450-5.

21. Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry. 1978;35(7):837-44.

22. Olafsdottir E, Aspelund T, Sigurdsson G, Thorsson B, Benediktsson R, Harris TB, et al. Unfavourable risk factors for type 2 diabetes mellitus are already apparent more than a decade before onset in a population-based study of older persons: from the Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik). Eur J Epidemiol. 2009;24(6):307-14.

23. Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, et al. Prevalence and correlates of diabetes in national schizophrenia samples. Schizophr Bull. 2000;26(4):903-12.

24. Leslie DL, Rosenheck RA. Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. Am J Psychiatry. 2004;161(9):1709-11.

25. Anderson SG, Livingston M, Couchman L, Smith DJ, Connolly M, Miller J, et al. Sex differences in plasma clozapine and norclozapine concentrations in clinical practice and in relation to body mass index and plasma glucose concentrations: a retrospective survey. Ann Gen Psychiatry. 2015;14:39.

26. Stroup TS, Gerhard T, Crystal S, Huang C, Olfson M. Comparative Effectiveness of Clozapine and Standard Antipsychotic Treatment in Adults With Schizophrenia. Am J Psychiatry. 2016;173(2):166-73.

27. Sharpe JK, Stedman TJ, Byrne NM, Wishart C, Hills AP. Energy expenditure and physical activity in clozapine use: implications for weight management. Aust N Z J Psychiatry. 2006;40(9):810-4.

28. Chen CH, Huang MC, Kao CF, Lin SK, Kuo PH, Chiu CC, et al. Effects of adjunctive metformin on metabolic traits in nondiabetic clozapine-treated patients with schizophrenia and the effect of metformin discontinuation on body weight: a 24-week, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2013;74(5):e424-30.

29. Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, et al. Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study. Am J Psychiatry. 2000;157(6):975-81.

30. De Hert M, Vancampfort D, Correll CU, Mercken V, Peuskens J, Sweers K, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation. Br J Psychiatry. 2011;199(2):99-105.

31. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380(9841):581-90.

32. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2013;1:CD004816.

33. Nielsen J, Røge R, Schjerning O, Sørensen HJ, Taylor D. Geographical and temporal variations in clozapine prescription for schizophrenia. Eur Neuropsychopharmacol. 2012;22(11):818-24.

34. Ringen PA, Engh JA, Birkenaes AB, Dieset I, Andreassen OA. Increased mortality in schizophrenia due to cardiovascular disease - a non-systematic review of epidemiology, possible causes, and interventions. Front Psychiatry. 2014;5:137.

Figure legends

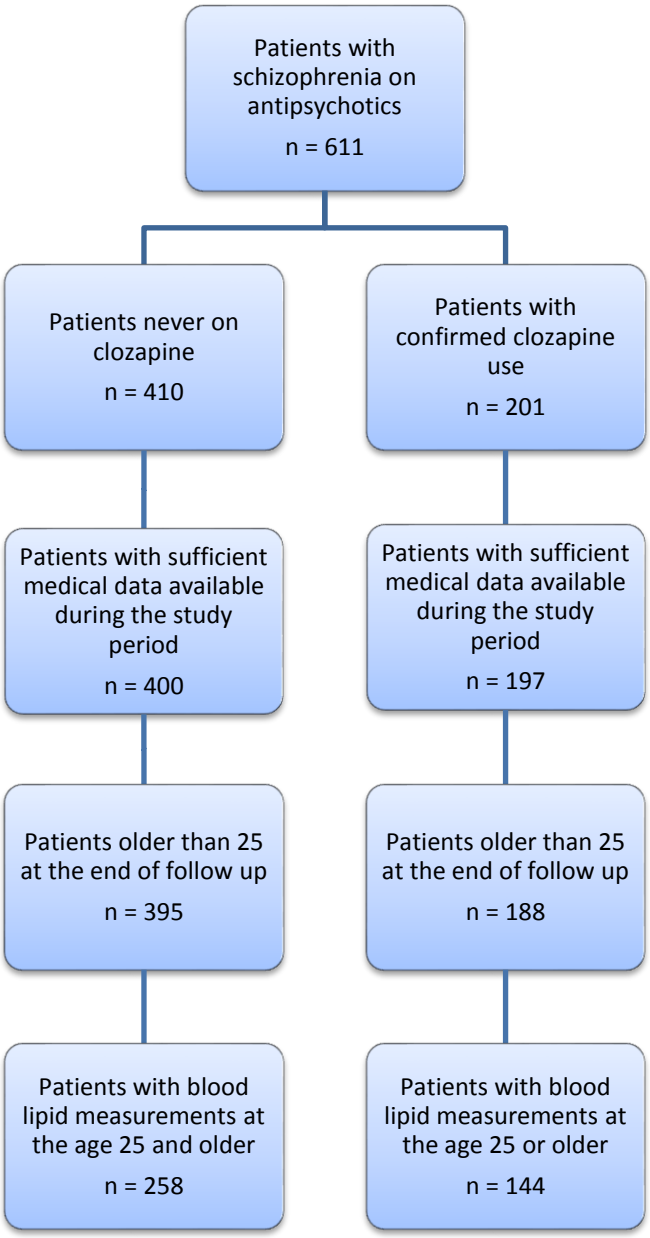

Figure 1. Description of study cohort in the study period of 1.1.1998 – 21.11.2014

Tables:

Table 1. Diabetes in patients with schizophrenia treated with clozapine and those never treated with clozapine

	Clozapine		Never-on-clozapine	
	Male (n = 132)	Female (n = 56)	Male (n = 245)	Female (n = 150)
Patients with type 2 diabetes (T2D)	18	9	31	23
T2D diagnosed before clozapine treatment	4	2	-	-
T2D diagnosed during clozapine treatment	11	5	-	-
T2D diagnosed after discontinuation of clozapine treatment	3	2	-	-
Patients with type 1 diabetes (T1D)	1	0	2	0
Patients with of T1D and T2D	19	9	33	23
Patients with a high risk of T2D (HbA1c in range of 6.0% - 6.4%)	13	9	15	8
Patients with T1D, T2D or a high risk of T2D	32	18	48	31
Prevalence of T2D	13.6%	16.1%	12.7%	15.3%
Prevalence of T1D, T2D or a high risk of T2D	23.5%	32.1%	18.8%	20.7%
Patients on metformin without a diabetes diagnosis	5	5	-	-
Mean age at end of follow up	50.0 (11.9)*	54.3 (11.4)*	56.7 (14.2)*	61.5 (16.1)*
Mean follow up period during clozapine treatment in years	9.3 (5.9)*	8.9 (5.6)*		
Mean follow up period in years			14.0 (3.9)*	13.5 (3.8)*

*Standard deviation

Table 2. Type 2 diabetes in patients with schizophrenia compared to Icelandic population controls, age and sex adjusted.

		Clozapine	Never-on-clozapine
Male			
	T2D	13.6%	12.7%
	Expected T2D from Icelandic population	5.8%	8.5%
	Standardized mortality ratio	2.3	1.5
	Confidence interval (95%)	1.4-3.5	1.0-2.0
	P-value	< 0.001	0.029
Female			
	T2D	16.0%	15.3%
	Expected T2D from Icelandic population	3.6%	5.5%
	Standardized mortality ratio	4.4	2.6
	Confidence interval (95%)	2.1-7.8	1.7-3.7
	P-value	< 0.001	< 0.001

Table 3. High blood sugar and ketoacidosis in patients with schizophrenia

	Clozapine n = 188					Never-on-clozapine n = 395				
Highest glucose measurement (mmol/l)	**13-20**	**20-30**	**30-40**	**40<**	**Ketoacidosis**	**13-20**	**20-30**	**30-40**	**40<**	**Ketoacidosis**
Glucose status										
Type 2 diabetes (n = 81)	7	1	2	0	0	14	12	0	3	0
Type 1 diabetes (n = 3)	0	1	0	0	0	1	0	0	0	1
High risk of type 2 diabetes (n = 45)	1	0	0	0	0	0	0	0	0	0
No glucose dysregulation (n = 454)	0	0	0	0	0	9	0	0	0	0

Table 4. Cox proportional hazards model with possible factors associated with glucose over 13 mmol/l

	Haz. Ratio	SE	z-score	95% CI	P-value
A. Male with glucose > 13 mmol/l					
Age	0.97	0.01	-2.38	0.94-.99	0.02
Clozapine	1.03	0.38	0.08	0.50-2.12	0.94
T2D	18.7	6.54	8.38	9.4-37.1	0.001 > p
B. Female with glucose > 13 mmol/l					
Age	1.01	0.02	0.47	0.97-1.05	0.64
Clozapine	0.62	0.47	-0.63	0.14-2.78	0.53
T2D	69.2	72.5	4.04	8.86-539	0.001 > p

A) n = 377, 39 cases. B) n = 206, 15 cases.

Table 5. Blood lipids in patients with schizophrenia both on clozapine and never on clozapine versus expected values from Icelandic population controls

		Clozapine	Expected from Icelandic population	P-value	Never-on-clozapine	Expected from Icelandic population	P-value
Male		n = 99			n = 175		
	Average age at last blood lipid test	47.7	-	-	54.4	-	-
	Average total cholesterol (mmol/l)	5.43	5.23	0.28	5.17	5.25	0.58
	Average LDL (mmol/l)	3.15	3.31	0.27	3.19	3.31	0.36
	Average total HDL (mmol/l)	1.21	1.31	0.04	1.26	1.33	0.10
	Average total triglycerides (mmol/l)	2.34	1.36	< 0.01	1.58	1.35	0.04
Female		n = 45			n = 83		
	Average age at last blood lipid test	51.9	-	-	58.0	-	-
	Average total cholesterol (mmol/l)	5.84	5.35	0.16	5.39	5.49	0.89
	Average LDL (mmol/l)	3.55	3.22	0.15	3.25	3.32	0.90
	Average total HDL (mmol/l)	1.40	1.65	0.01	1.40	1.66	0.34
	Average total triglycerides (mmol/l)	1.95	1.07	< 0.01	1.64	1.13	0.03